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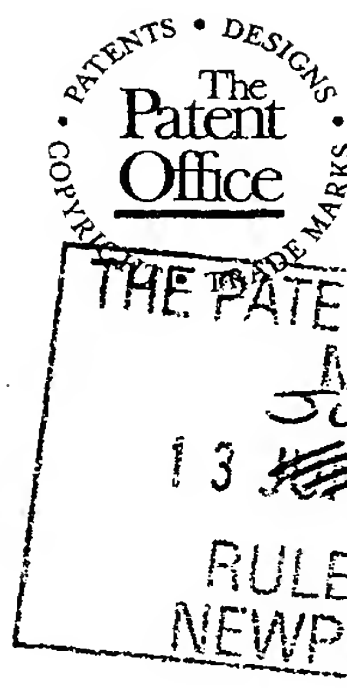
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Dated 27 June 2003



16 JUL 02 E733240-1 000319
P01/7700 0.00-0216311.1

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The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

KJL/CT/P5039

2. Patent application number

(The Patent Office will fill in this part)

13 JUL 2002

0216311.1

3. Full name, address and postcode of the or of each applicant (underline all surnames)

07865181001

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

Great Lakes (UK) Limited
Halebank
Widnes
Cheshire
WA8 8NS
United Kingdom

4. Title of the invention

An improved process for the production of substituted thioxanthenes

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Patents ADP number (if you know it)

ROYSTONS,

Tower Building,
Water Street,
Liverpool. L3 1BA
Merseyside.

1438001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
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Continuation sheets of this form

Description

6 ✓

Claim(s)

-

Abstract

-

Drawing(s)

-

10. If you are also filing any of the following, state how many against each item.

Priority documents

-

Translations of priority documents

-

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

-

Request for preliminary examination and search (*Patents Form 9/77*)

-

Request for substantive examination (*Patents Form 10/77*)

-

Any other documents
(*please specify*)

-

11.

I/We request the grant of a patent on the basis of this application.

Signature

Date

ROYSTONS

Roystons

12/07/02

12. Name and daytime telephone number of person to contact in the United Kingdom

K.J. Lees - 0151-236 9147/1417

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Notes

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Title: An improved process for the production of substituted thioxanthenes.

DESCRIPTION

The present invention relates to an improved process for the production of substituted thioxanthenes.

Various routes for the synthesis of substituted thioxanthenes have been described. See, for example, J. Chem. Soc. 1910 (97), 1297, Davis and Smiles; J. Chem. Soc. 1911 (99), 1355, Marsden and Smiles; J. Indian Chem. Soc. 1929 (6), 273, Sen and Sen-Gupta and WO97/49664, Anderson et al. Lambson Fine Chemicals Ltd.

Whilst conventional synthetic routes to substituted thioxanthenes are adequate, they do have a number of drawbacks. The routes can result in low yields of the desired product and/or mixtures of isomers and by-products that may be difficult to separate or purify. Thioxanthenes with side chains containing a chemically reactive group are conventionally made by further synthetic steps from the thioxanthone molecule and can involve two, three or four stages, resulting in the production of such molecules being a time consuming and inefficient process with low overall yields.

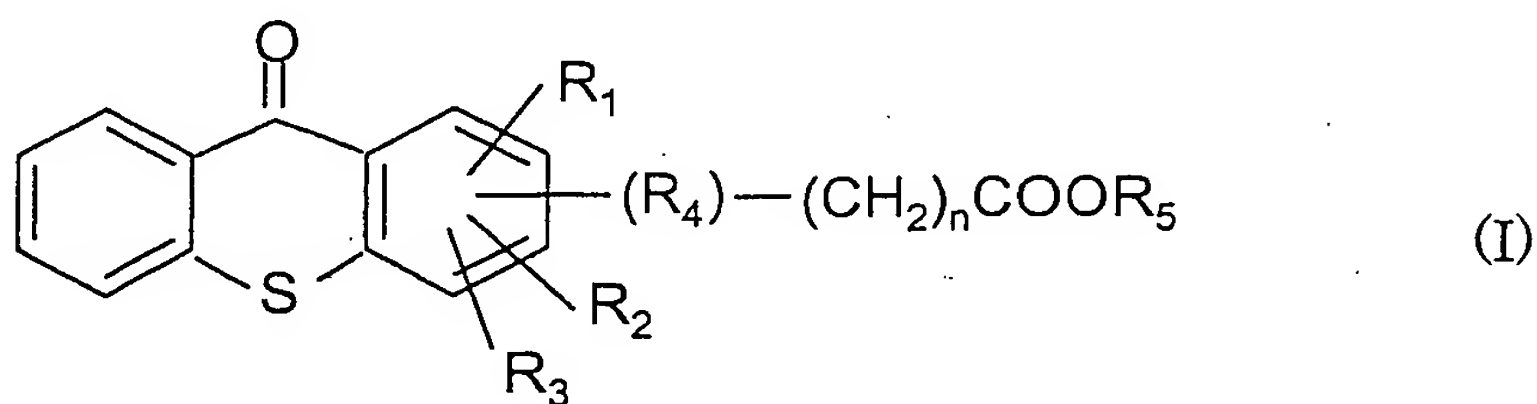
An example of a conventional synthetic route to 2-carboxymethoxythioxanthone involves three stages. Firstly, phenol is reacted with dithiobisbenzoic acid to produce 2-hydroxythioxanthone in a

60% yield. Secondly, the 2-hydroxythioxanthone is reacted with ethyl bromoacetate to produce the ethyl ester of 2-carboxymethoxythioxanthone in 75% yield. Thirdly, the ester is hydrolysed by acidification to produce the desired product in 90% yield. These three stages form an inefficient and time-consuming process to provide a product that is a dark colour, contains impurities and by-products and is produced with only an overall yield of 40% from the starting material.

Substituted thioxanthenes with side chains containing reactive groups are important intermediates in the pharmaceutical and photochemical industries. Therefore, an improved process for producing these intermediates in higher yields, with fewer steps and with less impurities would be desirable.

It is object of the present invention to provide an improved process for the production of thioxanthone derivatives containing side chains with chemically reactive side groups that aims to overcome, or at least alleviate, the above-mentioned drawbacks.

Accordingly, the present invention provides a process for the production of thioxanthone derivatives of the general formula (I) given below:



where:

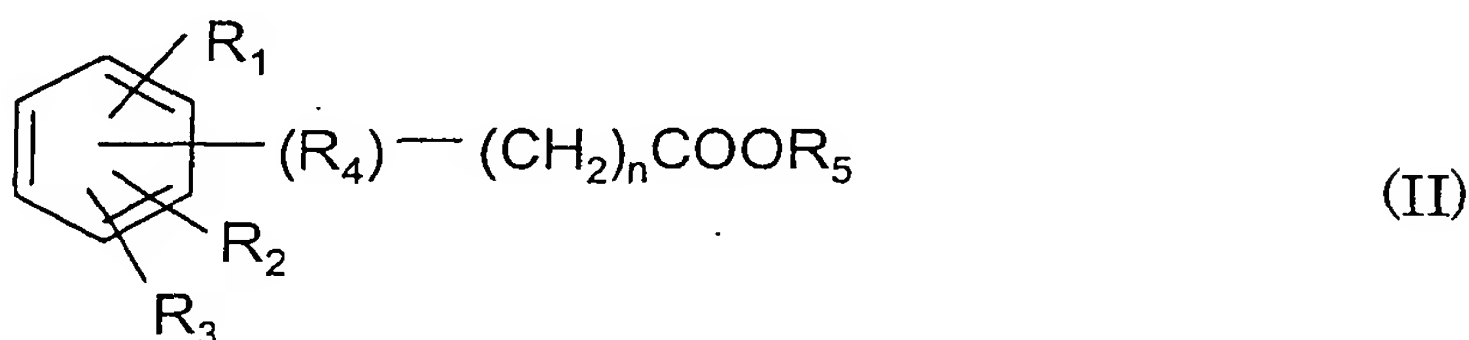
R_1 , R_2 and R_3 is hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, halogen, hydroxy or C_1 - C_2 dialkylamino; R_1 , R_2 and R_3 being the same or different;

R_4 is oxygen, sulphur or absent;

n is 0 to 10; and

R_5 is hydrogen, C_1 - C_{10} alkyl or aryl;

the one-step process comprising reacting a compound of given general formula (II) below with mercaptobenzoic acid or dithiobisbenzoic acid in the presence of sulphuric acid:



Preferably, the compound of formula (II) is phenoxyacetic acid, where R_1 , R_2 , R_3 and R_5 are each hydrogen, R_4 is oxygen and $n = 1$, thereby producing 2-carboxymethoxythioxanthone.

Preferably, the sulphuric acid is used in amounts of 1 part to about 20 parts by weight of acid to 1 part by weight of dithiobisbenzoic or mercaptobenzoic acid. The concentration of the acid is preferably greater than or equal to 90%.

The molar ratios of dithiobisbenzoic acid or mercaptobenzoic acid to a compound of formula (II) may vary between about 1:1 to 1:5.

Preferably, the reactants are stirred for a sufficient time to complete the reaction. The reaction temperature during the addition of the reactants is preferably in the range 0°C to 30°C but may be increased during the reaction from about 30°C to about 90°C. The reaction time is preferably 0.5 to 6 hours.

The product is preferably isolated from the reaction mixture by quenching with excess water and filtering the solid product. Preferably, water is added to dilute the acid strength to about 20 to 50%. The filtered product may be washed with water. The product may be further purified, if required, by means of crystallisation or slurry in an appropriate solvent.

The resultant thioxanthone compound is substantially free of impurities and may be provided in yields of up to 80%. Additionally, a single isomer is obtained.

The present invention will now be further illustrated by means of the following Examples in which Example 1 describes the synthesis of 2-carboxymethoxythioxanthone from dithiobisbenzoic acid according to the method of the present invention and Example 2 describes the synthesis of 2-carboxymethoxythioxanthone from mercaptobenzoic acid according to the method of the present invention.

Example 1.

The preparation of 2-carboxymethoxythioxanthone from dithiobisbenzoic acid.

Concentrated sulphuric acid (500g) and dithiobisbenzoic acid (30.6g) were charged to a reactor and phenoxyacetic acid (60.8g) was added over 1 hour keeping the temperature at 0-25°C. After stirring for 1 hour, water (470mls) was added. The solid product was filtered and washed with water (2x50mls). The solid was then stirred in 50% aqueous acetone (200mls) and heated to reflux for 0.5 hours. After cooling to ambient temperature the solid was filtered, washed with water and dried. 2-Carboxymethoxythioxanthone (43.4g) was obtained in 76% yield. This was a dull yellow solid, melting point 207 - 212°C. Assay by HPLC >97%. A single isomer was obtained.

Example 2.

The preparation of 2-carboxymethoxythioxanthone from mercaptobenzoic acid.

Concentrated sulphuric acid (250g) and mercaptobenzoic acid (15.4g) were charged to a reactor and phenoxyacetic acid (25.8g) was added over 1 hour keeping the temperature at 5-25°C. The temperature was raised to 50-60°C for 1 hour then water (270mls) was added. The solid product was filtered and washed with water (2x50mls). The solid was stirred in 120mls 50% aqueous acetone and brought to reflux for 0.5 hours. After

cooling to 15°C, the solid was filtered, washed with water and dried. 2-Carboxymethoxythioxanthone (13.5g) was obtained in 47% yield. This was pale yellow solid, melting point 210-215°C. Again, a single isomer of the product was produced.

The present invention enables a substituted thioxanthone compound to be provided that is substantially free of impurities and can be isolated in yields of up to, and possibly in excess of, 80% and as a single isomer.

This invention displays a yield from a single stage process that greatly exceeds that from alternative multi-stage conventional synthetic routes and provides material which is essentially free of impurities. The thioxanthone compounds so produced are useful as reactive intermediates in the pharmaceutical and photochemical industries.